

Remarks

Claim 1 has been amended in several respects:

1. The preamble has been amended to clarify that the composition is a “vaccine” composition and “one or more dosages” has been deleted and replaced with “a dose” following the comments regarding “multidose” compositions in the last Advisory Action. While the applicants traverse, they nevertheless amend claim 1 herein to recite a composition vaccine comprising “a dose,” which is believed to obviate the rejection.
2. “n” has been amended to be equal to or greater than 10. Support for this amendment is found in the paragraph bridging pages 6 and 7 of the specification.
3. Part (f) has been amended to clarify that the amounts of protein recited are of the conjugated protein. Support can be found in the specification at, for example, p. 5, ll. 15-36, p. 8, ll. 12-21, and p. 14, ll. 5-10.

The claims stand rejected for obviousness over several combinations of references. In brief, and as discussed more fully below, the claims are not obvious because:

- i. One of ordinary skill in the art at the time of the invention was someone involved in development of vaccines. Such a person had a natural reluctance to include more and different biological components into a vaccine composition because of the added complexity and consequent costs in developing and manufacturing a multicomponent vaccine, the uncertainty that the results would be both safe and effective, and the added complications of obtaining regulatory approval. And absent an identified deficiency and/or a convincing reason to employ an additional component, one of ordinary skill in the art would not do so.
- ii. The prior art fails to provide superior countervailing reasons to motivate one of ordinary skill in the art to overcome the natural reluctance to complicate a glycoconjugate vaccine with the addition of a second protein carrier, particularly where the carriers are Dt and Tt (as presently claimed).
- iii. There is no reason in the prior art to limit the amounts of Tt and Dt carrier in general to an amount of Tt less than or equal to 25 µg/dose or to an amount of Dt less than or equal to 60 µg/dose. The applicant was the first to recognize the problem that certain amounts of Tt lead to significant decrease of the immune response to the conjugated polysaccharide. Recognizing this problem led the applicant to the solution of using more than one carrier.
- iv. The prior art fails to recognize this problem caused by excessive carrier loading.

- v. The present claims are not a mere routine optimization of combining known prior art elements, as the Office has repeatedly alleged. The prior art provided no reasons or guidance to make the vaccine composition presently claimed. Merely because it would not require undue experimentation to make the claimed composition does not render the claims obvious. Patentability is not negated by the manner in which the invention is made. 35 USC § 103(a).
- vi. The results of making a multivalent glycoconjugate vaccine comprising Dt and Tt carriers were unpredictable at the time of the present invention. Because it was unrecognized that a reduction of the immune response to a conjugated polysaccharide would occur with excessive Tt carrier load, those of ordinary skill in the art could not have predicted that in certain circumstances, a multivalent vaccine composition comprising conjugated polysaccharide (glycoconjugates) in which two or more carrier proteins were employed as carriers would induce a greater immune response compared to a similar vaccine in which only a single carrier was employed.

1. One of ordinary skill in the art is a vaccine developer that has a natural reluctance to use more components than necessary in vaccines intended for commercialization

Obviousness must be considered from the perspective of the person of ordinary skill in the art.

Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.

Env'tl. Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696 (Fed. Cir. 1983) (citing *Orthopedic Equip. Co., Inc. v. All Orthopedic Appliances, Inc.*, 707 F.3d 1376, 1381-82 (Fed. Cir. 1983).

Submitted herewith is a Rule 132 Declaration of Dominique Schulz, who addresses these issues. As is clear from paragraphs 2 and 3 of D. Schulz's Declaration, she is and was in 1997 (when the priority application was filed) experienced in the technical field pertaining to the present claims, *i.e.*, vaccine development. Accordingly, D. Schulz is familiar with and well-qualified to address the factors that may be considered in determining the level of ordinary skill in the art.

As D. Schulz attests, the inventor, Dr. Odile Leroy, had MD and MPH (Master of Public Health) degrees, postdoctoral research experience, and more than five years of experience developing vaccines in the vaccine industry. One of ordinary skill in the art in 1997 was someone having an advanced degree in a scientific field relating to immunology and combating infectious disease and who had at least a view years of industrial experience.

D. Schulz attests that one of ordinary skill in the art would not only be aware of and influenced by scientific issues, but also by knowledge and factors specific to vaccine developers including industrial scale manufacturing concerns and the demand of the Regulatory Authorities.

As D. Schulz further attests, a vaccine cannot be brought to market without receiving governmental regulatory approval. Regulatory requirements are even more demanding for vaccines compared to conventional (i.e., small molecule) pharmaceuticals because vaccines are biological products that are administered to healthy people, including in the case of the present vaccine, healthy children. Consequently, a vaccine developer must generate accurate data from both clinical trials and physical and functional characterization. In practice, this means that each time a new component is added to a vaccine, additional trials and assays on both the component and combination vaccine are necessary. And each new assay adds to the expense, development time, and the number of variables that can go wrong.

Furthermore, D. Schulz attests that one of ordinary skill in the art would be cognizant of scientific hurdles that could be encountered in developing a vaccine. D. Schulz further attests that they occur on an unpredictable basis and that one of ordinary skill in the art would primarily proceed on an empirical basis when developing a new vaccine.

D. Schulz further attests that one of ordinary skill in the art would have been aware of that the consequences of error could be serious from both the clinical and commercial perspective and was only heightened by the knowledge that vaccines such as those presently claimed were for pediatric use, including administration to healthy infants.

For the foregoing reasons, D. Schulz attests that the vaccine developer of ordinary skill in the art had to justify each component proposed for inclusion in a new vaccine, which would mean that the potential benefits would have to outweigh the increased development and manufacturing complexity with their attendant costs, the uncertainties regarding safety and efficacy, and the enhanced difficulties in obtaining regulatory approval.

D. Schulz attests that as a result, vaccine developers in 1997 (as today) would have and did proceed very slowly, generally following two fundamental principles: (a) follow proven vaccine development strategies if possible, and (b) use the fewest number of biological components necessary for the vaccine's intended purpose.

As a result, D. Schulz attests that those of ordinary skill in the art seeking to develop a *Streptococcus pneumoniae* glycoconjugate vaccine would look to approved vaccines for guidance. By 1997, four glycoconjugate vaccines had been approved, all of which were anti-*Haemophilus influenzae* (Hib) vaccines. D. Schulz attests that, accordingly, one of ordinary skill in the art contemplating a new *Streptococcus pneumoniae* glycoconjugate vaccine would have turned to these approved vaccines for guidance.

Furthermore, D. Schulz attests that were a vaccine developer to decide on employing the glycoconjugate approach, once a particular carrier protein/conjugation strategy had been proven to be safe and immunogenic in the target population and received regulatory approval, one of ordinary skill in the art would have sought to stick with it and not change strategy absent a very strong and well defined motivation to do so.

Lastly, D. Schulz attests that she, who was active in the field of vaccine development in 1997, is and was unaware

- (a) of any vaccine in development at that time employing more than a single protein carrier;
- (b) of any well-defined and convincing reasons for employing more than a single carrier; and
- (c) of any contra-indications for use of a single carrier.

As a result, D. Schulz attests, employing a second carrier in a vaccine composition would have been inconsistent with the general practice of those of ordinary skill in the art at the time.

It is against this backdrop of level and knowledge of one of ordinary skill in the art that obviousness must be determined.

2. The prior art fails to provide advantageous reasons to make the presently claimed composition that outweigh the added costs, manufacturing complexity and associated risks that would be associated with including more than one carrier protein into a multivalent glycoconjugate vaccine.

As described above, the person of ordinary skill in the art was strongly motivated to keep vaccine compositions as simple as possible to facilitate manufacturing and regulatory approval and to avoid risks associated with complicating a vaccine with additional components. Consequently, for the present claims to have been obvious, not only must there have been some foreseeable advantage in combining Dt and Tt carrier proteins in a multivalent pneumococcal

conjugate vaccine, but the deficiencies in the simpler approach of using only a single carrier must have also been manifest and of such a nature that the ordinary artisan would have a reason to accept the foreseeable increased complexity in development and manufacturing, the uncertainties regarding safety and efficacy, the additional regulatory burden, and the added costs associated therewith of using Dt and Tt as carrier proteins in a single composition. The evidence of record (in the form of D. Schulz Rule 132 Declaration) is that there were no well-defined and convincing reasons to employ two carriers rather than one and no known contra-indications for using a single carrier. None of the art presently being cited by the Office provides such a reason. Before the present application, there was no glycoconjugate vaccine in development comprising more than one carrier protein (let alone Dt and Tt, as presently claimed), which D. Schulz's Declaration confirms.

Chu *et al.* (Infection and Immunity, 40(1):245-56, April 1983) is the main art the Office relies on to reject the claims that disclose administration of two glycoconjugates each coupled to a different protein carrier. But Chu *et al.* is, at its heart, a pure academic scientific, paper and not at all concerned with the regulatory constraints faced by vaccine developers. And while those of ordinary skill in the art would not have ignored the teachings of Chu *et al.*, they would have taken its teachings in the context of the commercial and regulatory constraints within which they acted and, as a consequence of the reasons discussed more fully above and those discussed below, would have attributed little if any significance to it.

As evidence of this, the applicant notes that Chu *et al.* was published in 1983, yet there is no subsequent report of any multivalent glycoconjugate vaccines employing more than one carrier before the present application was filed some 14 years later. Given the dire human need for effective vaccines (including against *Streptococcus pneumoniae*) recognized by those skilled in the art during that time frame and the consequent market pressures brought to bear on them, this is additional evidence that Chu *et al.* had little if any influence in guiding those of ordinary skill in the art towards employing more than a single carrier in a multivalent glycoconjugate vaccine.

Importantly, Chu *et al.* indicates that there is no advantage of combining glycoconjugates with different carriers.

After testing the immunogenic response in mice to a combination of Hib-TT and Hib-HCH glycoconjugates, Chu *et al.* reported the following on page 249, col. 2, lines 8-17:

The effect of injecting both Hib conjugates [*i.e.*, Hib-TT and Hib-HCH] was similar to that observed with the monovalent preparations. The total Hib polysaccharide dose was 2.5 µg in the mice receiving either the monovalent or the bivalent preparations. There were no differences between the anti-Hib antibodies in the groups that received both Hib conjugates after any of the three immunizations by using the criteria of either the GM or the percentage of responders.

And on page 253, first sentence of the paragraph bridging the columns, Chu *et al.* teaches:

No advantage upon anti-Hib antibody formation was achieved by using the K100 conjugates alone or in combination with Hib-HCH.

The applicant acknowledges that while Chu *et al.* also teaches that when Hib-HCH was injected with either Pn6A-HCH or Pn6A-TT, both the anti-Hib and anti-Pn6A responses were increased over that induced by either conjugate alone. But the possible explanations of this phenomenon are completely independent from the carriers, as Chu *et al.* itself acknowledges on page 253, 1st col. (emphasis added):

One explanation for this enhanced anti-Hib and anti-Pn6A response was that the total amount of the cross-reacted polysaccharides was two times (5.0 µg/dose) then that injected with either conjugate alone. The steep dose-response curve observed for the Hib conjugates makes this a possibility. Another explanation for the enhancement in the antibody responses to both polysaccharides elicited by their simultaneous administration as conjugates may be due to the cross-immunogenicity between the Hib and Pn6A polysaccharides reported in hyperimmune animal sera, but hitherto unreported in humans.

It is significant that the authors themselves do not even conjecture that carrier proteins may play any part in the enhanced response.

In view of the foregoing, the applicant respectfully submits that Chu *et al.* provides **no** basis that would give a reason to one of ordinary skill in the art to combine Dt and Tt glycoconjugates, let alone a basis that outweighs the strong reluctance of those of ordinary skill in the art to add to the complexity of a vaccine composition and incur the concomitant increased development and manufacturing complexity, uncertainties in safety and efficacy, enhanced regulatory burden, and the attendant costs thereof.

In addition to Chu *et al.*, three other pieces of prior art were cited: Each of European Patent Application No. 0 497 525, May 8, 1992 (the '525 publication), Ahman (Pediatr. Infect. Dis. J., 15, 134-9 (1996)), and Anderson (J. Pediatrics 128, 649 (1996)) relate to vaccine compositions comprising multiple pneumococcal glycoconjugates, each glycoconjugate comprising a different pneumococcal polysaccharide and the same protein carrier.

The '525 publication is concerned mainly with improved methods of making glycoconjugates. The Examples of the '525 publication describe *Streptococcus pneumoniae* glycoconjugates in which the carrier protein is OMPC (outer membrane protein complex) or a subunit thereof (MIEP). None of the examples describes multivalent *Streptococcus pneumoniae* glycoconjugate vaccines. Mixtures of *Streptococcus pneumoniae* glycoconjugates are mentioned in the general description (pp. 50-51) but do not appear to have been made or tested and, more importantly, contemplate only a single carrier. There is nothing in the '525 publication that would suggest and more importantly, give reason to one of ordinary skill in the art to use more than one protein carrier in a multivalent *Streptococcus pneumoniae* glycoconjugate vaccine.

Nor is there anything in Ahman et al and Anderson et al. that would give reason to one of ordinary skill in the art to partially substitute another carrier for the single carrier used in the pentavalent and heptavalent pneumococcal glycoconjugate vaccines they respectively disclose (Ahman et al uses CRM197 and Anderson et al uses OMPC as single carrier) to form a several carrier glycoconjugate vaccine.

None of the art would have indicated to the ordinary artisan any deficiency in multivalent pneumococcal glycoconjugate vaccines having a single protein carrier. Without an identified deficiency, there could have been little if any reason to increase the complexity of multivalent *Streptococcus pneumoniae* glycoconjugate vaccines by using several carriers instead of one and, by the same token, increase the complexity of the registration procedure before the Regulatory Authorities.

Furthermore, it is significant to note that in 1997 there was not even one approved multivalent *Streptococcus pneumoniae* glycoconjugate vaccine comprising a *single* carrier. To suggest that one of ordinary skill in the art would jump to a multivalent *Streptococcus pneumoniae* glycoconjugate vaccine comprising *two* carriers without the existence of an approved multivalent *Streptococcus pneumoniae* glycoconjugate vaccine comprising even *one*, and without persuasive evidence that the benefits of employing two carriers would outweigh the uncertainties in safety and efficacy, the increased development and manufacturing complexity, the more burdensome regulatory process, and the added costs associated therewith, is completely contrary to the knowledge and practice of those of ordinary skill in the art as set forth in D. Schulz's Declaration.

3. **The applicant was the first to recognize that using a single Dt or Tt carrier in a multiple glycoconjugate vaccine may lead to a negative interference phenomenon and the first to recognize the solution of employing more than one carrier.**

The present application discloses for the first time that exceeding certain Tt and Dt carrier protein limits in a glycoconjugate vaccine can result in negative interference, *i.e.*, the carrier protein load can reduce the anti-polysaccharide antibody response to the administered glycoconjugates.

The Israeli and Finnish clinical trials that led to this discovery were supported and directed by a predecessor company of the current assignee, Sanofi Pasteur, and disclosed *for the first time* in the data presented in the tables on page 4 of the specification. Tetravalent pneumococcal glycoconjugate vaccines using either Tt or Dt as the sole carrier and increasing amounts of conjugates (expressed by the polysaccharide amount) – and consequently of the carrier – were administered together with a Hib glycoconjugate (PRP-Tt) vaccine.¹

The data show that increasing amounts of Tt carrier resulted in reduced antibody response to PRP and that this negative interference was dependent on the load of carrier protein administered.

Accordingly, the applicant was the first to recognize that a significant diminution of the immune response to the polysaccharide component of a glycoconjugate begins once the total load of protein carrier exceeds a threshold amount, and, consequently, the applicant was the first to recognize the solution that the amount of protein carrier in a glycoconjugate vaccine could be maintained at these low levels without decreasing the desired amount of polysaccharide by using more than one protein carrier: “In order to overcome the problem which the phenomenon of negative interference constitutes in a multivalent vaccines composed of glycoconjugates, the present application proposes to use not one but at least two carrier proteins so that the maximum load of each of the carrier proteins is not reached.” Specification p. 4, ll. 16-22.

In Dagan *et al.* Infect. Immun. (May 1998) 66 (5) : 2093, which post-dates the present application, the present inventor and her co-authors elaborate on the Israeli and Finnish clinical studies first reported on pages 3 and 4 of the present specification.² Figure 1 of Dagan *et al.*

¹ These glycoconjugate vaccines were administered simultaneously with DTP vaccine and either with or without oral or injectable polio vaccines.

² In preparing the present Response, the applicant discovered a clerical error in the specification, which reports that the serotypes used in the Israeli and Finnish studies were 6B, 9V, 18C, and 23F. In fact, the serotypes

presents a graphic representation of the data from the Finnish study reported on p. 4 of the present application:

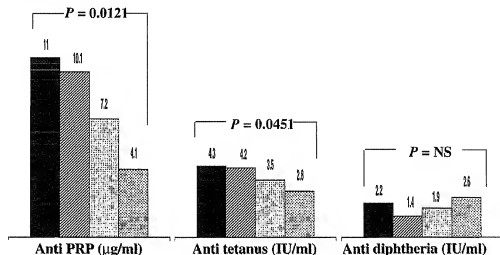


FIG. 1. Anti-PRP, antitetanus, and anti-diphtheria toxoid antibodies after the third injection of one of the various doses of PncT: placebo (PncT₀) (■); tetraivalent PncT vaccine, 1 μg of each polysaccharide (PncT₁) (▨); tetraivalent PncT vaccine, 3 μg of each polysaccharide (PncT₃) (▧); and tetraivalent PncT vaccine, 10 μg of each polysaccharide (PncT₁₀) (▩). NS, not significant.

As seen in the left-most figure, which graphically displays the data presented in the first table on p. 4 of the specification, the anti-PRP antibody response dropped about 8% (from 11 μg/ml to 10.1 μg/ml) when the PncT tetraivalent pneumococcal conjugate vaccine (1 μg of each polysaccharide) was added to the PRP-Tt conjugate, amounting to 33 μg Tt carrier per dose (See foot-note below table 2. This calculated amount is fully explained in a subsequent paragraph). A reduction of about 35% is seen when the polysaccharide dose was 3 μg (Tt carrier ~ 48 μg per dose). Finally, a 63% reduction is seen at the 10 μg dose (Tt carrier ~ 96 μg per dose).

With the Dt conjugated pneumococcal vaccine a different pattern was seen: there is no negative interference at either the 1 or 3 μg dose (Dt ~ 8 and 24 μg respectively), but at the 10 μg dose (Dt ~ 80 μg) there is a noticeable (35%) reduction in the anti-PRP antibody response (see table 1 of page 4 of the specification).

As shown in the specification, table 2, the Israeli study also shows negative interference. At the 3 μg dose (Tt ~ 24 μg and Dt ~ 24 μg respectively) both the Tt and Dt conjugated pneumococcal vaccines negatively interfere with the anti-PRP response. No dose-dependent relationship can be observed because the results of only one dose are reported.

used were 6B, 14, 19F, 23F, as reported in Dagan *et al.* The applicant submits that this error does not change the

On page 4 of the specification, it is also reported that a similar interference effect with Dt as carrier was observed in a clinical study in Iceland in which infants received PRP-Dt instead of PRP-Tt.

Dagan *et al.* additionally present a more detailed scientific analysis of the negative interference phenomenon, on page 2096, 2nd col :

It is thus of primary importance to analyze possible interference between conjugates that share the same carrier moiety. In the present study, such an issue was addressed for infants who received either the DTP or the PRP-T vaccine alone or together with a vaccine containing pneumococcal polysaccharide antigens conjugated to TT or diphtheria toxoid. Our results clearly showed that the anti-PRP antibody response decreased significantly when the PRP-T conjugate was administered together with DTP and the tetravalent PncT conjugates. This decrease was dose dependent and also affected the anti-tetanus antibody response. Notably, this suppression was carrier specific, since it was more accentuated with increasing load of TT and was not observed after simultaneous administration of PRP-T with pneumococcal polysaccharide conjugated to diphtheria toxoid.

Additional support for the suggestion that TT overload interferes with the anti-PRP antibody response can be derived from the finding that when PncT₀₃ (tetravalent PncT vaccine with 3 µg of polysaccharide of each serotype) was administered to Israeli and Finnish infants, the interference with the anti-PRP antibody response was more accentuated in the Israeli group (Israeli DTP contains twice the concentration of TT as Finnish DTP).

These observations, which could not have been made before because the relevant data were not previously available, led the present inventor to the discovery that more than one carrier protein could be advantageously used to avoid the negative interference phenomenon due to Tt / Dt overload.

Furthermore, the prior art gave no reason to select the particular amounts of Tt and Dt recited in the present claims. This is not surprising given that the prior art did not recognize the problem that increased carrier load could lead to decreased anti-polysaccharide antibody response.

Claim 1 recites that the total amount of Tt carrier present in the claimed composition does not exceed 25 µg/dose and the total amount of Dt carrier does not exceed 60 µg/dose. The technical significance of these figures is confirmed by Dagan *et al.* In the footnote to Table 2,

substantive teachings of the application.

Dagan reports the following amounts of Tt in the various vaccine components used in the Finnish trial:

DTP	15 µg
PRP-T	24 µg
PncT ₀₁	9 µg
PncT ₀₃	24 µg
PncT ₁₀	72 µg

So, in the trial in which PncT₀₁ was administered and a modest decrease of about 8% in the anti-PRP response was observed, the total conjugated Tt was $9 + 24 = 33$ µg and the total Tt (conjugated and free) was $33 + 15 = 48$ µg.

Because the immunosuppressive effect of Tt carrier load accelerates with increased amounts of Tt (note the nearly 30% decrease in anti-PRP antibodies for PncT₀₃), the value of 25 µg of conjugated Tt per dose as recited in the specification and claims represents an approximate value of technological significance above which the detrimental effect of the conjugated carrier protein load begins to become substantial.

4. The prior art fails to recognize the problem of negative interference that may arise upon administration of multivalent glycoconjugate vaccine using a single carrier

As noted above, the present inventor was the first to discover that administration of multivalent glycoconjugate vaccines can lead to a decrease of the anti-polysaccharide antibody response due to Tt/Dt carrier protein overload. This became possible only after data were generated measuring the antibody response to polysaccharides as a function of Tt/Dt carrier load. Such data were first reported in the present application and subsequently in Dagan *et al.* None of the art relied on by the Office in rejecting the claims as obvious includes such data or the recognition of the phenomenon. As previously noted, none of the art indicates any deficiency in multivalent glycoconjugate vaccines having a single protein carrier.

5. The presently claimed compositions are not merely the result of routine optimization

The Office has on several occasions pointed to prior art multivalent pneumococcal vaccines, both non-conjugated and conjugated, as evidence that it is a routine matter to combine different glycoconjugates (with a single carrier). But that certain successes exist only establishes

that it is not impossible to combine multiple glycoconjugates with a single carrier. Such successes do not demonstrate that combining such elements was routine. Indeed, notwithstanding those successes, the prior art still emphasized the uncertainty and potential pitfalls associated with combining multiple valences and glycoconjugates, as evidenced by the passages from Klein *et al.* (Microbial Drug Resistance, 1(1):49-58, 1995), WO 00/56360, and de Velasco, Microbiological Reviews, 59: 591-603 (1995) set forth in the applicant's after-final response filed April 6, 2009, and hereby incorporated by reference.

Furthermore, the case law cited by the Office does not support its basis for rejection. On page 5 of the final Office Action, the Office stated:

The combination [of the cited art] teaches all the carriers and polysaccharides, exemplifies with two different carrier proteins and it would have been obvious to combine different conjugates conjugated to the recited different carriers identified by Merck and Co. Inc. *As set forth supra*, the number of known carrier proteins were articulated by the art. The polysaccharides were articulated by the art, the means of conjugation was known to the art and the effect of carrier proteins were known to the art. Therefore the selection of carrier proteins, their dose and the ratio of polysaccharide to carrier proteins are well within the skilled artisans grasp. . . . As the dose of carrier protein and the ratio of polysaccharide to carrier protein were known to affect immunogenicity, it would have been obvious to optimize the doses of the chosen carrier proteins, Dt and Tt and any of the others articulated by the art.

Similar comments were made on page 3 of the final Office Action. The Office maintained that the present claims are merely a result of routine optimization. The applicants respectfully traverse. The claimed subject matter is more than merely routine optimization of a result oriented variable. The present claims comprise a new combination of components (*i.e.*, a glycoconjugate vaccine comprising Tt and Dt carrier proteins). The case law relied upon by the Office relating to optimization is inapposite to such a situation. In *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 10 USPQ2d 1843 (Fed. Cir. 1989), the prior art patent taught combinations of diuretics and the claims at issue comprised the selection of two of the disclosed diuretics combined in a specified ratio. Thus, the claims at issue were a species of a prior art genus, and the claims were obvious absent some unexpected properties.

But in the present case the prior art does not disclose glycoconjugate vaccines comprising a genus of protein carriers from which the present inventor merely selected Dt and Tt and optimized the amounts of each to be used. As previously argued, absent a recognized deficiency in current vaccines and/or an expected overriding benefit, one of ordinary skill in the art would

have been reluctant to use more than one carrier in a multivalent glycoconjugate vaccine because of the added costs, manufacturing complexity and associated risks and increased regulatory complexity.

And in *In re Boesch*, 205 USPQ 215 (C.C.P.A. 1980), also cited in the final Office Action, the prior art actually suggested the sort of optimization undertaken to arrive at the claims at issue. That is not the situation here.

Furthermore, the Office's approach in rejecting the present claims is contrary to *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673] (Fed. Cir. 1988), relied with approval recently in *Bayer Schering Pharma AG v. Barr Laboratories Inc.*, 91 USPQ2d 1569 (Fed. Cir. 2009), where the court stated that a claimed invention is not obvious simply because it may have been obvious to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, [but] where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Id.* at 1573-74. Nor would a claimed invention have been obvious where vague prior art does not guide an inventor toward a particular solution. *See Id.* at 1574. But this is precisely what the Office is doing in the present rejection.

The Office asserted that all the components and general methods for conjugation were known in the art and, further, that carrier protein dose and ratio of polysaccharide to protein were known "to affect" immunogenicity. But this is simply insufficient under *O'Farrell* because the cited art neither gave direction to which of many possible combination of parameters would likely give a successful result, nor did the art guide the inventor toward the particular solution presently being claimed. In fact, the art could not have guided the ordinary artisan to the particular solution because the problem (*i.e.*, decreased polysaccharide response with increased Tt/Dt carrier load) was not known until presented in the instant application. And while the polysaccharide dose and polysaccharide/protein carrier ratio were known "to affect" immunogenicity, that "affect" was not specific enough to guide one of ordinary skill in the art to the presently claimed solution, and, accordingly, the Office has not otherwise articulated how such "affects" would have guided one to the particular combination of components recited in the present claims. And, furthermore, this does not even take into account that one of ordinary skill in the art had a natural reluctance to go in the direction of the presently claimed compositions for the reasons set forth in D. Schulz's Declaration and above.

The cited art does not assist in overcoming these deficiencies. Ahman *et al.* states, “Little is known about the optimal composition of conjugate vaccines.” p. 137, 2nd col.

The Examiner refers to Klein *et al.* for its unfortunately ambiguous statement, “At the present time, all of the vaccine manufacturers are aiming to produce pneumococcal conjugate vaccines that contain between seven and nine serotypes conjugated to one or several different carrier proteins.” The applicants respectfully submit that the Office has used hindsight to misconstrue this statement, which, when read in isolation, is ambiguous. The applicants submit that one of ordinary skill in the art would understand this statement to mean not that vaccine manufacturers were testing conjugate vaccines containing several different carrier proteins in the same vaccine but that any one particular manufacturer was either testing a single carrier protein in all its multivalent conjugate vaccines (e.g., CRM 197 by Praxis, *see* Table 6 of Klein) or that it was testing several carrier proteins, but each in a different vaccine (e.g., Tt and Dt by Pasteur/Merieux/Connaught, *see* Table 6 of Klein). That is, the reference to “seven and nine serotypes conjugated to one or several different carrier proteins” is a reference to how many carrier proteins (one or several) were being tested by each manufacturer, not how many were in a single vaccine.

That one of ordinary skill in the art would understand Klein’s statement in this manner is manifested by reading the statement in the context of the entire Klein paper and the knowledge of those of ordinary skill at the time of the present invention. On p. 53 of Klein, in the section entitled, “Laboratory and Clinical Studies,” Klein describes Table 6 as presenting vaccines currently in development. All are vaccines having a single carrier protein. But, as noted above, some manufactures (e.g., Praxis) were pursuing vaccines with a single type of carrier protein while others (e.g., Pasteur Merieux Connaught) were using multiple carriers in the development of their vaccines, each vaccine with a different (but only one) carrier. Indeed, in the mid-nineties, the assignee³ was developing two octavalent pneumococcal glycoconjugate vaccines; one using only Tt and the other using only Dt as carrier.

Furthermore, had Klein intended to refer to multiple carriers in a single vaccine, one would have expected a more elaborate discussion of it rather than merely a passing mention

³ The assignee of this application is Sanofi Pasteur SA, which in the mid-nineties had the registered name of Pasteur Merieux sérums et vaccins and commercial name of Pasteur Mérieux Connaught and subsequently changed to Aventis Pasteur and then to Sanofi Pasteur SA.

given that Klein is a review article discussing all aspects of pneumococcal conjugate vaccines and the use of multiple carriers in a single vaccine would have been an noteworthy feature.

In addition, a 2002 review of the state of pneumococcal vaccines by Wuorimaa and Kayhty (Scand. J. Immunol. **56**, 111-129 (2002); copy enclosed) further supports the view that Klein's statement was not referring to multiple carrier proteins in a single vaccine. Table 1 of Wuorimaa lists numerous pneumococcal conjugate vaccines with 7 to 9 serotypes as referred to by Klein, but all contain only a single carrier protein; Wuorimaa discloses no vaccines with 7 to 9 serotypes conjugated to more than one carrier in a single vaccine.⁴ So, Wuorimaa supports the applicants' construction of Klein's statement, too.

The applicant furthermore notes that Klein's statement is not a teaching or suggestion to use the particular carrier proteins recited in the present claims, Dt and Tt, together in a single vaccine. This is significant because, as Klein noted (and quoted above), Dt and Tt may "affect carrier priming as a result of prior or co-administration of unconjugated carrier proteins (e.g., diphtheria toxoid) that are often part of other childhood vaccines (e.g., DTP)."

The foregoing demonstrates that when taken in context with the knowledge of those of ordinary skill in the art at the time, the ordinary artisan would not read Klein's statement as meaning that glycoconjugate vaccines with multiple carriers were being developed.

The deficiency in the obviousness rejections under *O'Farrell* for failing to identify in the art a reason and/or guidelines to combine the vaccine components as presently claimed is also manifest when one considers that under the Office's reasoning it would have been equally obvious to combine 10 or more *Streptococcus pneumoniae* polysaccharide-Tt glycoconjugates in a single vaccine (i.e., a glycoconjugate vaccine comprising only a single Tt carrier). But, as the calculations below demonstrate, were one to do that based on the teachings of the cited art, one would arrive at vaccine compositions having an amount of Tt far greater than the 25 µg/dose recited in the claims:

1. Chu *et al.*

Chu *et al.* employed a 2.5 µg dose of polysaccharide "chosen on the basis of previous experiment and because this amount of conjugate seemed compatible with

⁴ The only examples of the use of multiple carrier proteins in the same vaccine are for 11-valent vaccines and all post-date the present application.

proposed dosage in human infants.”⁵ And in Table 1,⁶ Chu *et al.* also teaches that the ratio TT protein : polysaccharide (TT Prt:PS) for the pneumococcal-tetanus toxoid glycoconjugate (Pn6A-TT) was 1.7. So, a dose of Pn6A-TT containing 2.5 µg Pn6A would contain 2.5 µg • 1.7 (TT Prt)/PS= 4.2 µg of TT protein. So, a combination of 10 different pneumococcal-TT glycoconjugates, each at a dose of 2.5 µg of serotype polysaccharide (as recommended by Chu *et al.*), comprises 10 • 4.2 µg TT protein = 42 µg TT protein.

2. EP 497 525

The examples of the ‘525 publication describe pneumococcal PS-OMPC glycoconjugate solutions containing an average of 5 µg protein for 1 µg pneumococcal PS as determined from the protein : PS ratio calculated from the reported values of mg/ml PS, mg/ml protein, and/or PS:Protein:

Example	Conjugate	PS (mg/ml)	Protein (mg/ml)	PS:Protein	Protein:PS (calculated)
5	Pn6B-OMPC	0.33	2.2	0.15	6.6
7	Pn14-OMPC	0.39	1.3	0.30	3.6
9	Pn23-OMPC	0.28	2.025	0.14	5.3
25	Pn18-OMPC	0.34	2.57		5.3
27	Pn4-OMPC		0.92	0.23	4.3

Mono- and multi-valent pneumococcal glycoconjugate vaccines in the 1994-1997 time frame generally employed at least about 1 µg polysaccharide of each serotype (and frequently more).⁷ This combined with the ‘525 publications teaching of an average of about 5 µg protein per µg polysaccharide would lead one seeking to create a 10-valent vaccine to employ 10 polysaccharide serotypes • 5 µg protein/polysaccharide serotype = 50 µg protein.

3. Ahman *et al.*

Ahman *et al.* teaches a pentavalent vaccine with the following characteristics:⁸

⁵ Page 247, 2nd col, in the section entitled “Immunization.”

⁶ Page 249, 1st col.

⁷ See the table in the Exhibit appended to this response, which reports amounts of glycoconjugated pneumococcal polysaccharides employed in 16 different mono-and multi-valent vaccines.

⁸ Page 135, 1st col., penultimate paragraph entitled, “Vaccines.”

Conjugate	PS (µg/dose)	PS/Prot ratio	Protein (µg) (calculated)
6B-CRM	10	0.4	25
14-CRM	10	0.65	15.3
18C-CRM	10	0.9	11.1
19F-CRM	10	0.33	30
23F-CRM	10	0.58	17

Total: 98.4

Were one to follow Ahman *et al.*'s teachings with regard to the amounts of pneumococcal polysaccharide and protein to employ, substitute TT for CRM as the carrier, and use 10 pneumococcal serotypes rather than the five reported, one would arrive at a vaccine having well over 100 µg TT per dose.

4. Anderson *et al.*

Anderson *et al.* describes a heptavalent pneumococcal glycoconjugate vaccine containing 11 µg PS and 85 µg protein carrier (OMPC) per dose : "Each 0.5 ml dose contained 3.5 µg of type B polysaccharide, 2 µg of type 19F, 1.5 µg of 9V and 1 µg of each of the other polysaccharides, with a total of 85 µg of outer membrane protein complex."⁹

In view of the teachings of the present specification and Dagan *et al.*, following the teachings of each of Chu *et al.*, EP '525, Ahman *et al.*, and Anderson *et al.* would result in a composition that would induce an anti-*Streptococcus pneumoniae* polysaccharide immune response *far smaller* than would be induced by were the amount of conjugated Tt held below 25 µg/dose, as presently claimed, because the amount of Tt in decavalent glycoconjugates following these teachings would be far in excess of 25 µg/dose. Thus, the presently claimed vaccine compositions exhibit properties different from other similar compositions that are "obvious" under the Office's reasoning, but the Office has failed to identify any teachings in the prior art that would have permitted the ordinary artisan to predict such a difference. The present claims are non-obvious for this reason as well.

⁹ Page 650, 1st col. last paragraph

6. The properties of the claimed vaccines were not predictable

The Office maintains that the claims are merely a combination of known elements yielding the predictable result that the polysaccharide moiety of the glycoconjugates present in the composition would be immunogenic. The applicants respectfully disagree. For the reasons explained above, the combination of Tt and Dt protein carriers in amounts less than recited in the claims avoids the risk of a negative interference phenomenon between glycoconjugates. Thus, in view of the data and analysis presented in Dagan *et al.*, one of ordinary skill in the art would expect that the claimed compositions would induce an enhanced immunogenic response to the conjugated polysaccharides compared to an equivalent vaccine having a single protein carrier. This property was not predictable from the prior art because, as explained above, it was unknown that increased loads of Tt/Dt carrier in multivalent glycoconjugate vaccines, for example, could detrimentally affect the immune response to some of the polysaccharides.

7. Response to Advisory Action

In addition to the foregoing, the applicant maintains and reiterates the arguments presented in their after-final response filed April 6, 2009. While the arguments in that response and the present paper address most of the Office's comments in the Advisory Action mailed April 20, 2009, the applicant adds the following.

The Advisory Action stated, "That the experimentation would be extensive does not make it undue or provide for a lack of expectation of success, especially in view of the fact that several vaccine conjugates of polysaccharide and pneumococcal polysaccharide in particular were known to the art and successful at providing for vaccination." The applicant submits that it is because several pneumococcal conjugate vaccines were known in the art to be successful at providing for vaccination that contributes to the non-obviousness of the presently claimed compositions. As argued previously, the pressures on those of ordinary skill in the art were to maximize the simplicity of a vaccine and stick with tested and proven methods. The fact that pneumococcal conjugate vaccines were known to be successful would give reason to the ordinary artisan not to complicate such a vaccine by adding a second carrier.

In responding to the applicant's argument concerning reasonable expectation of success, the Office stated,

This is not persuasive because the art of record at the time the invention was made did provide for a reasonable expectation of success and Klein et al teaches that practical limits indicate that the conjugate vaccine have less than the 23 carbohydrates. It is noted that the Klein et al directs the skilled artisan to less than 23-way vaccine, but does not teach that such would not be effective to provide for immunization, but indicates that there is doubt to improvement of the 23-way vaccine when read in context.

(Emphasis added.) Two points are to made in response. First, the expectation of success referred to in this passage relates to multivalent conjugate vaccines with a single carrier. Second, and moreover, if there is doubt to the improvement of the 23-way vaccine there would be no reason to complicate it by adding a second carrier and thereby increasing the costs and regulatory burdens.

The Office argued, “the problem [of carrier suppression] was clearly known and the solution was to use multiple carriers....Applicants ignore that the solution of combining carriers in mixed vaccines was a known solution to the carrier suppression....[T]he use of multiple carriers was known.” The applicant disagree. None of the art upon which the claims are rejected teach or suggest benefits to employing multiple carrier proteins in a single vaccine composition in order to obviate or minimize the problem of carrier suppression. While Chu *et al.* teach glycoconjugate compositions comprising two carriers (but not both Tt and Dt), the results, even with the benefit of hindsight, remain ambiguous and, therefore, do not suggest clear benefits from combining multiple carriers. The applicant respectfully requests that the Office specifically identify such teachings if they exist.

The Office stated, “Applicants arguments that the ‘wisdom in the art’ was to avoid Dt and Tt [flies] in the face of the [successful] vaccine of Ahman et al at the time of the invention.” The applicants respectfully disagree. The vaccine of Ahman employed a single carrier protein, CRM₁₉₇, a mutant Dt.

The Office repeatedly noted that the claims are not limited to Dt and Tt carrier proteins. The applicant agrees but notes that Dt and Tt are required carriers in the claimed vaccine compositions and, therefore, to render the claims obvious the prior art must at least render obvious conjugate vaccine compositions comprising both Dt and Tt, with or without additional carriers.

The Office stated,

Applicants argue that the only examples of multiple carrier proteins and multiple serotypes are post-filing. This is simply not true for carriers in genera and saccharides in general and Applicants are directed to the combination of carriers and saccharides in general. Applicants would have one believe that they were the first to combine different carriers and different saccharides. This is simply not so, while they may be the first to combine Dt and Tt [pneumococcal] conjugates, the art of record clearly indicates that they were not the first to combine different carriers and different polysaccharides in the same vaccine formulation.

Either the Office is obfuscating the distinction between free and conjugated carrier protein, or it is misstating the facts. Other than *Chu et al.*, which has been discussed, none of the art upon which the present claims are rejected teaches a single conjugate vaccine formulation having two or more protein carriers conjugated to different polysaccharides. If the applicant is incorrect on this point, the Office is respectfully requested to identify by page and line number where such a formulation is disclosed.

In response to the applicant's argument that non-obviousness is supported (not proved, but supported) by the passage of 100 years since conjugates were first discovered, the Office stated, "it has not been 100 years since discovery and implementation (see Ahman and Anderson of record). The fact that one did not implement Applicants invention does not mean that it was unobvious." The applicant first apologizes for a factual error. As explained by D. Schulz, conjugates were first discovered and reduced to practice in 1929, so it was nearly 70 years (not 100) years since the discovery of conjugates until the time that a conjugate vaccine with two or more carriers was first disclosed (by the present application). Ahman and Anderson both disclose conjugate vaccines with a single carrier. While the passage of 70 years may not *prove* non-obviousness, as the Office asserted, it is *strong evidence* in support of it.

And in response to the assertion that the fact that the present invention was not previously implemented does not mean it is not obvious, the applicant does not rely on this fact to prove non-obviousness but relies on it in combination with the other reasons presented herein and before as strongly supporting non-obviousness.

Conclusion

In view of all of the foregoing arguments and those in the applicant's after-final response, the applicant respectfully submits that the claims as amended are in condition for allowance.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: March 3, 2010

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